Symptoms, Signs and Findings in Humans Exposed to PCBs and Their Derivatives

by G. Reggiani* and R. Bruppacher*†

The records of the health effects caused by some accidental exposure and findings from medical examination in cases exposed to polybrominated biphenyls (PBB) as well as to polychlorinated biphenyls (PCB) and their derivatives polychlorinated dibenzofurans (PCDF) and dibenzodioxins (PCDD) have provided some information for the recognition and classification of their toxicity in humans.

The most impressive clinical features have been presented by the Yusho episode of exposure. Dermatologic signs are the most persistent indicator of a considerable uptake. Neurological symptoms, respiratory findings and impairment of liver function are further aspects of the contamination. Skin manifestations have been observed also in the newborn infants from mothers exposed to high levels of the substances.

However, the available data make it still hard to assess the clinical picture of the effects on humans in cases of acute exposure and even more the effects on reproduction and long-term effects. Furthermore it would still be arbitrary to draw a line between the symptoms which can be referred to PCBs and PBBs alone and those which can be related qualitatively and quantitatively to PCB derivatives (PCDFs, PCDDs, PCQs).

Introduction

PCBs had and still have a large variety of applications, mainly in high voltage electronic tools. They are not counted among the most toxic chemicals but, because of their resistance to degradation in the environment, their concentration in the food chain and their persistence in the human body, they present an increasing problem as a contaminant and raise questions as to possible effects on the health of our population.

The human organism may be confronted with PCBs and their derivatives in various ways: during the namufacturing of PCBs (mainly in the chemical industry), during the manufacturing of goods containing PCBs (mainly in the electric industry but also in the production and during use of paints, plastics and carbonless copy paper), in a contaminated environment and through consumption of contaminated food. All these situations can occur in a controlled (chronic) or an uncontrolled (acute, accidental) way.

Literature is growing, both on the prevalence and on possible health effects of man's exposure to PCBs. Occupational exposure and the contamination of environment and food have become subjects of intensive investigations. These epidemiologic studies together with a steadily improving capacity to measure low levels of PCBs and their contaminants in the environment as well as in tissues of animals and man will certainly lead to a much more precise assessment of the risks of these compounds to human health in the future. Today, however, our knowledge of the clinical toxicity of these compounds and their derivatives still is derived mainly from observations after accidental and high level exposure. In these cases, however, attention was often focused only after health effects were noted; consequently the assessment of exposure was late and incomplete.

We are confronted, also in the case of the PCBs, with the usual difficulties of clinical toxicology. We usually have only very limited knowledge of the duration and the intensity of exposure, on the route of administration and the latency period to the onset of clinical effects. Because the population is involved accidentally, the kind and number of cases are the result of circumstances and many other factors remain uncontrolled that determine the availability of the substance in the body as well as the susceptibility of the individual and thus the health effects. Finally, we usually have no baseline data.

In the case of the PCBs we have the additional complication that they represent a group of chemicals with different characteristics regarding metabolism and specific toxicity. Furthermore, the situation is complicated by contamination with other much more toxic compounds, especially the benzofurans.

With respect to the other contributions at this work-shop, we shall confine ourselves to a presentation of the clinical picture observed after exposure to PCBs. The kinetics of the substance and the epidemiologic aspects,

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*F. Hoffman-La Roche & Co., CH-4002 Basel, Switzerland.

†Author to whom correspondence and reprint requests should be sent.

Table 1. Ingestion of PCB and contaminants by Yusho cases: Japan 1968.

	Average daily dose, mg	Average total dose, mg
PCBs	1.9–8.4	500–805
PCDFs	0.01–0.04	3.2–4.4
PCQs	1.7–7.2	450–756

are presented elsewhere (1–3). In the order of their contribution to clinical toxicological knowledge the overview will include observations after accidental high level exposures, chronic occupational exposure and only touch on exposure through food and environment. The picture presented must be selective and cannot be complete, but we hope that it will contain the outlines most important to the clinicians.

Episodes of Accidental High Level Exposures

Yusho/Yu-Cheng

Much of our knowledge of the effects of PCBs and their contaminants in the human body still is derived from the so-called "Yusho" episodes. Approximately 1600 residents were exposed to a mixture of polychlorinated biphenyls, polychlorinated dibenzufurans (PCDFs) and polychlorinated quaterphenyls (PCQs) in 1968 in western parts of Japan. They had consumed rice oil contaminated with Kanechlor 400, a heat transfer medium, and developed severe clinical symptoms (4–7). A similar event occurred in 1978 in Central Taiwan, where 2000 residents were exposed to a similar mixture of PCBs, PCDFs and PCQs (8,9). The clinical symptoms observed (called Yusho for the Japanese occurrence and Yu-Cheng in the Taiwanese cases) have become a kind of a reference profile for intoxications involving PCB mixtures, because the data available from these two episodes still are the most precise information we have about the daily intake, length of exposure and total dosage, as well as on the latency to onset of effects and time of the appearance of the single symptoms and signs of the clinical picture of such a poisoning.

Doses ingested during several months in the Japanese Yusho cases are given in Table 1, and the resulting clinical symptoms, signs and findings are summarized in Table 2. Skin and ocular manifestations were the most dominant. They diminished gradually over the next ten years (10). The same pattern of ocular manifestations has also been reported in the Taiwanese cases (11). Symptoms of the nervous system and disturbances of the liver function were less frequent and less severe. Chronic bronchitis correlated with PCB concentrations in sputum and blood and persisted in 20% of the cases for more than ten years. A threefold increase in triglycerides serum levels returned to normal after 5–7 years.

Irregular menstrual cycles were noted in 60% of the exposed women of child bearing age.

Table 2. Yusho cases, Japan, 1968–1970: clinical symptomatology.

Symptoms and signs	% showing or reporting
Dermatological manifestations[a]	82–89
Acneform eruptions	
Distinctive hair follicles	
Red plaques on limbs	
Dark brown pigmentation of nails, skin, mucuous membranes	
Itching and sweating of palms	
Ocular manifestations	83–88
Eye discharge	
Swelling of upper eyelid	
Hyperemia of conjunctiva	
Cyst formation of tarsal glands	
Pigmentation of eyelid	
Pigmentation of conjunctiva	
Transient visual disturbance[b]	
Neurologic/gastrointestinal/muscular	
Hearing difficulties	18
Headaches, vomiting, diarrhea	17–39
Numbness of limbs, weakness, muscle spasm	32–39
Sensory and motor conduction	9
Respiratory/immunologic	
Chronic bronchitis[c]	40
PCB in sputum	
Lower serum Iga and IgM levels	
Hepatic and metabolic	
Jaundice[d]	10
Elevated serum triglycerides (3-fold)[e]	
Reproductive	
Irregular menstrual cycles	60
Fetal/newborn (babies exposed in utero, $N = 13$)	
Stillbirths ($N = 2$)	
"Cola colored" ($N = 1$)	
Low birth weight	
Elevated bilirubin	
Conjunctivities	
Enlarged Meibomian glands	
Chloracne	
Dark brown pigmentation of skin (groin, gums and nails)	
Hypoplastic nails	
Scalp calcification, natal teeth ($N = 2$)	
Retarded growth (several years)	
"Soft" neurologic signs (at age 7–9)	

[a] Diminishing gradually over the next 10 years; some subcutaneous cyst formation persisting.
[b] In some cases still present after 10 years.
[c] Severity correlated with PCB blood level.
[d] No liver function abnormality in most cases.
[e] Normal after 5–7 years.

Low birth weight, elevated bilirubin, conjunctivitis, enlargement of Meibomian glands, hypoplastic nails, dark-brown pigmentation of skin, gums, nails and groin, which gradually faded, retarded growth for a few years (12) and abnormal number and shape of teeth were observed in the newborns from exposed pregnant women. Some developed chloracne. "Soft" neurological signs were observed at ages 7 to 9 (13).

Similar symptoms were observed among the exposed Taiwanese population.

The latency period of clinical symptoms was around two months in the Japan episode; in the Taiwan episode

it was 2.7 months. A detailed account of the symptomatology of the two Yusho episodes has been given in an earlier paper (14).

The Michigan PBB Incident

Three commercial products, hexa-, octa-and decabromobiphenyl, known under the tradenames of Firemaster, Bromkal and Flammex, have been used mainly as flame retardants until 1974, when their production was stopped in the U.S. (15). They are of interest in the toxicology of halogenated biphenyls, because they were the main factors in another episode of considerable proportions.

In 1973, a mixture of the three polybrominated biphenyls was mixed accidentally into animal feed (Nutrimaster) in a factory of the Michigan Chemical Corporation, whereby 1000–2000 lb of a fire retardant was added to the livestock food supply of Northern Michigan. The accident was revealed by adverse health effects observed in the cattle in several dairy herds: milk production decreased, the cattle lost weight and developed abnormal hooves with lameness; abortions occurred also in swine. Animals sent to slaughter presented enlargment of the liver. PBB levels in the feed ranged from 2.4 to 4300 ppm, in contaminated milk from 2.8 to 270 ppm.

Until the affected herds and flocks were quarantined in spring 1974, over 10,000 Michigan residents were exposed to PBB through the consumption of milk, meat and other dairy products. Blood levels measured in two

samples of this population were significantly higher in the people from quarantined farms as compared to those from the nonquarantined farms, although low levels were observed also in the first group.

Health complaints, such as numbness, stomach pains, headache, fatigue, anxiety and abnormal liver function tests in people exposed were reported. The Michigan Department of Health undertook a series of studies in summer and autumn 1974. In a group of 300 exposed people who had worked or lived in the quarantined farms for six months or more since the accident, no unusual abnormalties of the heart, liver, nervous system, urinalysis, blood counts and all other medical conditions examined could be found, which did not occur also in a matching control group. Several of the exposed women delivered normal babies. PBB levels in blood and breast milk were higher, but there was no relationship with complaints or abnormal medical condition.

Three years later another study on more than 3300 persons included groups with different levels of exposure. PBB serum levels were highest in plant workers manufacturing PBB ($\bar{x}$ = 108.7 ppb) and lowest in a volunteer group ($\bar{x}$ = 3.2 ppb). Other groups corresponded to the estimated level of exposure. There was no positive association between serum concentration of PBB and reported symptom or disease frequencies (16,17).

Several retrospective studies were concerned with specific symptomatology. Skin manifestations reported by Chanda (18) are summarized in Table 4. Bromacne was observed in 13% of 53 Michigan chemical workers. It was the only sign of exposure in these cases with the highest PBB blood levels.

The route of exposure (contact and inhalation) might be an explanation for the surprising absence of other skin lesions noted in the Michigan farmer population and even in the controls taken from farms in Wisconsin. With the exception of bromacne, there is hardly any difference in prevalence of objective signs between the quarantined and nonquarantined farms for itching, dryness and folliculitis, not even with the control group, and there was no positive correlation between these skin lestions and serum PBB levels.

Neurological symptoms were the object of a similar study of 664 Michigan farmers including 153 Wisconsin

Table 3. Michigan PBB incident: symptoms and conditions by PBB serum level.[a]

Symptom reported (incidence in %) by ca. 3300 subjects	Serum PBB concentrations, ppb						
	0	1	2–3	4–9	10–19	20–99	100+
Skin rash (7.8)	9.0	8.5	8.4	7.2	8.3	6.3	4.1
Fatigue (38.3)	46.5	40.1	40.7	38.1	37.8	28.7	27.4
Joint pains (28.6)	42.9	32.7	29.8	26.4	28.4	21.6	17.1
Hepatitis (1.4)	4.5	1.4	1.8	1.4	1.3	—	—
Diabetes (2.4)	4.7	2.9	2.4	1.8	1.9	3.3	—
Benign tumors (0.6)	—	0.9	0.5	0.5	1.0	0.4	1.8
Cancer (all) (5.3)	2.7	7.5	5.6	4.3	5.3	3.8	2.6

[a] Data of Budd et al. (16).

Table 4. Michigan PBB incident: skin symptomatology.[a]

	Quarantined farms (N = 485)	Nonquarantined farms (N = 299)	Plant workers (N = 53)	Controls (N = 228)
Serum PBB (ppb)	21	4.2	123	—
Symptoms				
Peeling and scaling	17	18	—	9
Erythema	11	13	—	5
Hair loss	13	11	—	5
Nail growth	7	11	—	—
Sweating	21	24	—	13
Itching and dryness	31	32	—	29
Folliculitis	23	24	—	30
Bromacne	2	5	13	—

[a] Data of Chanda et al. (18).

dairy farmers as controls (19). Subjective neurologic symptoms were found more frequently among the Michigan population, but the serum PBB levels did not correlate with subjective and objective neurological symptoms. A negative correlation was found, however, between performance test scores and the blood chemistry abnormalities (increased SGPT and SGOT) observed in the exposed group.

A study of the immunocapability in 41 cases with high serum PBB levels (7300 ppb), in 56 cases with levels of 1 to 9, and 7 cases with levels less than 1 ppb showed no difference in the lymphocyte count or functions (17). However, 15% of the exposed persons were found to have two or more abnormalities of in vitro lymphocyte functions.

A second study of the immune capacity was performed in 45 adult dairy farm residents of Michigan who consumed PBB-contaminated food for a period of 3 months to 4 years in comparison to control groups of farmers in Wisconsin and residents of the New York area. The Michigan group showed a significant decrease of T- and B-lymphocyte subpopulations in 35% of the cases and impaired lymphocyte function, i.e., decreased response to mitogens (20). The analysis of the clinical history of the symptoms and biochemical abnormalities in the exposed farmers did not reveal any increase of acute or chronic minor or major infections (21).

Human studies have largely failed to demonstrate a clear-cut pattern of illness common to PBB-exposed persons. There are, also, different views about the more subtle neuropsychologic effects in the offspring (22), and results of the investigations of developmental abilities remain controversial, too (23,24).

Other Incidents

Another accident involving animal feed occurred through a transformer leak in a hog processing plant in Montana, which lead to a widespread contamination with PCBs; this episode, however, remained without clinical consequences (25).

The clinical observations after chemical fires are difficult to separate from the general effects caused by smoke and fumes (26). Transformer and capacitor fires are extensively covered elsewhere (27–29).

Chronic Occupational Exposure

Reports on effects of occupational exposure date farther back (30), but the Yusho episode has directed attention again to the possible health effect of occupational exposures to PCBs.

In Japan, a 20–30% incidence of dermal symptoms, consisting of "distinctive hair follicles and pimple-like skin eruptions" in exposed areas such as the face, neck and forearm was reported among employees in a capacitor factory (31). They had used pentachlorobiphenyls and Kanechlor 300. After 1972, when the use of PCB was suspended, skin findings abated. Persons working in environments that contained 0.02–0.3 ppm of PCBs showed "brown chromodermatosis" and "acneform exanthema" of hands and fingers and nail bed and comedos or acneform exanthema of the jaw, back and thighs. These signs disappeared one month after stopping handling of PCBs. In another factory with environmental concentrations of 0.002 ppm no dermal manifestations were observed (32).

Ouw and colleagues (33) reported complaints of a burning sensation of the face and hands, nausea and a persistent body odor in a study of 34 workers exposed to Aroclor 1242 in a capacitator manufacturing plant in Australia. One had chloracne and five suffered from an eczematous rash on the legs and hands. Although hepatic function tests were normal, the mean blood Aroclor level in the exposed group (400 ppb) was significantly higher than in a control group of 30 unexposed volunteers.

A study of 5 workers using Aroclor 1016 from a capacitator manufacturing plant in New York State by Alvares and co-workers (34) did not reveal acneform skin lesions or other clinical manifestations suggestive of PCBs toxicity. Liver and kidney function tests, serum electrophoresis, triglycerides and cholesterol levels were within normal limits. Nerve conduction velocity studies gave normal results. Nevertheless he noted significantly lower half lives of antipyrine (10.5 hr vs. 15.6 hr in nonexposed controls) and an increased metabolic clearance rate suggesting a barbiturate type of inducing drug metabolism in man which could also be demonstrated in animal experiments.

A detailed picture of clinical manifestations in workers exposed to dielectric fluids containing PCBs was elaborated during a clinical field survey of 326 capacitor manufacturing workers by Fischbein and colleagues and reported in great detail (35,36). Of the subjects examined, 90% were employed for more than 5 years, 40% for 20 years or longer. Reported symptomatology was dominated by dermatological symptoms: mainly a skin rash (39%), a burning sensation (25%) and acne (11%). However, the prevalence of reported pigmentation disturbances, thickening of the skin and discoloration of the nails, generally considered to be typical of PCB poisoning, was markedly lower (3%). On physical examinations almost 40% presented abnormalities including erythema, swelling, dryness and thickening. 6% were found to have acneform eruptions, and 15% showed conjunctival and palpebral abnormalties including palpebral hyperpigmentation and edema. Abnormal secretion from the eyes and the typical enlargement of the Meibomian glands were seen in 2% respectively 1%.

Neurologic symptoms were cited by 39% of the males and 58% of the female workers. They included headache, dizziness, depression, sleeplessness, nervousness, fatigue, somnolence and memory loss. But routine neurologic examination did not reveal any remarkable prevalence of abnormalities.

Gastrointestinal symptoms like anorexia, weight loss, nausea, vomiting and abdominal pain were reported by

13% of the male and 23% of the female workers and muscle and joint pain also was indicated twice as often by women (15%) than by men (8%).

Upper respiratory irritation was indicated by 48%, and a history of tightness in the chest was given by 10% of the group. In 14% the forced vital capacity was less than 80% of the value predicted and in 11% a restrictive impairment was diagnosed. X-rays of the lung were normal except in one case.

Laboratory examination yielded generally normal results of biochemical and hematological tests. Both for lower and higher homologs of PCBs, a good correlation of mean plasma levels with the history of exposure was noted. However, no association was found between reported symptoms and duration of employment. There was also no correlation between reported symptomatology and plasma levels of lower or higher homologs of PCBs. On examination only dermatologic findings showed a correlation and this with the higher homologs of PCBs in blood. Of the laboratory tests SGOT levels did correlate with both lower and higher homologs of PCBs.

In another survey conducted by the U.S. Center for Disease Control and the National Institute for Occupational Safety and Health in three groups of workers occupationally exposed to polychlorinated biphenyls, no clinical abnormalities attributable to exposure to PCB could be observed, while symptoms suggestive of mucous membrane and skin irritation of systemic malaise and altered peripheral sensation were indicated more freqently by persons with higher concentrations of serum PCBs. Positive correlations were also found with lower enzyme activities, glutamic-oxalacetic transaminase (SGOT), serum gamma-glutamyl transpeptidase (GGTP), and plasma triglycerides. The high density lipoprotein-cholesterol showed an inverse correlation with plasma PCB (37).

In Italy, Maroni and colleagues (38) investigated 80 workers (40 males and 40 females) exposed to Pyralene 3010 or to Apirolio in capacitor manufacturing and testing plants (both PCB mixtures contain 42% chlorine). Absorption had occurred mainly through the skin. Fifteen workers were found to have skin diseases; of these four had chloracne, four folliculitis, one oil dermatitis, one juvenile acne and five dermatitis due to irritative or allergic agents; 16 workers showed hepatic involvement, consisting most often of hepatomegaly with an increase in serum lower enzyme levels (GGT, AST, ALT and OCT). All of these were men. In two workers, bleeding cavernous hemangiomas were discovered, in one case associated with chronic myelocytic leukemia. No definite association was found between chloracne and blood PCB concentrations but particularly trichlorobiphenyl blood concentrations correlated significantly with abnormal liver findings which were considered as clinical signs of hepatic microsomal enzyme induction.

The demonstrated long-term toxic effects, including liver tumors and other liver diseases, in exposed laboratory animals (39–42) has prompted a retrospective

cohort mortality study of 2567 workers with a total experience of 39,018 person years in two plants who were employed for at least 3 months in areas where PCBs were used. Mortality from all causes and from cancer was lower than expected (163 vs. 182.4 and 39 vs. 43.8 respectively). Excess mortality was noted for cancer of the rectum, of the liver and to a less degree, of the breast. None of these excesses were statistically significant. Earlier reports of an increase of cancer of the pancreas, of lung cancer and of melanoma could not be confirmed. Experiences on long-term effects, however, is still very limited.

Exposure of the General Population

Through routine waste disposal or accidental leakage polychlorinated biphenyls are now widely distributed in the environment. Like TCDD residues they are accumulated and concentrated by fish and non occupational human exposure to PCBs occurs now primarily through the diet.

Relations with PCB levels or with clinical symptoms are, however, difficult to establish even in situations where the contamination is unusually high. Use of sewage sludge containing close to 500 ppm of PCBs for gardening purposes was not significantly associated with PBC-blood levels and no clinical signs of PCB toxicity could be noted (43). There was no relation to haematologic, hepatic or renal function tests. However, plasmatriglyceride levels increased significantly with serum PCB concentration indicating that PCB may alter lipid metabolism at levels of exposure and bioaccumulation insufficient to produce overt symptoms. In a survey of a community in Alabama, known for unusually high DTT exposure, average blood levels of 17.2 ppb were found (44). They were positively related to age, even when controlled for other variables associated with PCB level: sex, local fish consumption, obesity, serum cholesterol levels, and alcohol consumption. No major point source of PCB contamination could be found and fish taken in the drainage of a major population center had mean PCB levels below the then in force FDA tolerance of 5 mg/kg. PCB levels were positively associated with γ-glutamyltranspeptidase, serum cholesterol and blood pressure. The blood presure association was independent of age, sex, body mass index and social class. An association with triglycerides could not be found, and an inverse association with high-density lipoprotein-cholesterol could not be confirmed either. However, this again raises the question about the long-term implication with respect to cardiovascular disease.

There are numerous other studies on PCB levels and health findings in the general population. Relationships however, are usually erratic and difficult to interpret. On the other hand, PCB levels were examined in populations with specific complaints. Berovici and Wasserman (45) found, e.g., higher PCB serum levels in comparison with a control group in 7 out of 15 cases of

missed abortions and in 8 out of 17 women with premature delivery.

The newborn and infant may be more exposed because the only way to excrete large amounts of PCBs is through lactation. In a recent study in Michigan reported by Wickizer and co-workers (46), 1057 breast milk samples tested contained at least trace amounts but up to 5.1 ppm on fat weight basis of PCB residues. Although there is no clear indication that this level of contamination poses significant health hazards to the infant, it does give reason for concern. Wickizer repeats the earlier advice of the American Academy of Pediatrics (47) that the breast milk of nursing mothers with potentially high exposures to PCB should be tested and breast feeding should be limted in mothers whose milk fat is found to be highly contaminated.

Contaminants

Polychlorinated dibenzofurans (PCDFs) are formed in the commercial synthesis of PCBs, they are structurally and toxicologically similar to the chlorinated dioxins and concentrate likewise in the liver as well as to a lesser degree in the adipose tissue. The 2,3,7,8-tetrachlorodibenzofuran is the most toxic of the PCDFs and orders of magnitude more toxic than PCBs. It has a similar structure as the corresponding polychlorinated dibenzodioxin 2,3,7,8-TCDD (48). Rather high quantities of PCDFs have been found in Yusho oil and in the tissues of people who had suffered Yusho disease.

Polychlorinated dibenzodioxins (PCDDs) are usually discussed in connection with herbicides, fungicides and as a contaminant of the production of chlorophenols. Others are formed during the combustion of chlorinated hydrocarbons, also of chlorobenzenes used together with PCBs in transformers and capacitors. The clinical observations after exposure to PCDDs, particularly 2,3,7,8-TCDD, are the subject of an extensive literature summarized elsewhere (49).

Summary and Conclusions

It is not easy and not really possible to put the findings described in the literature into a simple and comprehensive picture. Such a picture must be somewhat arbitrary, in view of the often conflicting reports and the difficulties of observational experience described above.

By far the most impressive clinical picture is presented by the Yusho cases. This, however, is very likely due to the contaminants and not only to the PCBs themselves. The route of exposure and absorption as well as the level of exposure have been often advocated as a possible explanation for the discrepancy between the clinical picture reported in cases of occupational exposure (mainly through skin and inhalation) and in cases of accidental exposure (mainly through the gastrointestinal tract). Yet in the final analysis it is the chemical which is circulating in the blood stream, stored in the fat tissues, muscle, bones and organs which is determinant for the toxicity.

Blood levels are highest in the occupationally exposed; however, they are often difficult to correlate with the clinical findings. Such a lack of correlation is well known in clinical pharmacology for many lipophilic substances (e.g., Vitamin A). Blood and tissue levels are necessary to determine that the person has actually taken up the substance and not only had the chance to do so. The contrast to the background level and thereby the quantitative aspect may be of use in determining the uptake in a specific situation.

Dermatologic signs are the most impressive indicator of a considerable uptake. Pigmentation and ocular symptoms are frequently seen in poisonings where PCB is involved but probably are due to the contaminants. The same is true for chloracne, where the benzofurans probably are mainly responsible in the Yusho cases. At least, chloracne is relatively specific for a small group of chemicals. Cases of chloracne and bromacne among workers exposed to PCBs and PBBs for longer periods have been observed, but there seems to be no correlation between duration and level of exposure, blood concentration and clinical picture. Skin manifestations heal slowly (48) in about 80% of the cases. In some cases, sequelae remain which can be detected clinically when other symptoms and signs have disappeared.

Although there may be a notable increase in the prevalence of subjective neurologic symptoms (headache, dizziness, fatigue, nausea and vomiting) or of peripheral nerve symptoms (like numbness, joint and muscle pains), they are so frequent in control subjects that they are of little significance to the clinician.

More impressive are the respiratory findings in high level exposure, however there are usually many confounding influences. Impairment of other physiologic functions, such as the liver, fat and porphyrin metabolism are less frequent and less severe. In high-level exposure, peripheral neuropathies, liver function impairment, and increase of serum triglycerides return to normal after a few months to a few years after exposure has ceased, depending on the severity of the poisoning. The correlation with blood fat levels and blood pressure in the general population with PCB levels is interesting but needs further confirmation.

Increased enzyme activity and drug metabolism was observed in cases where clinical history and physical examination revealed no acneform skin lesions or other manifestations suggestive of PCB toxicity. The clinical consequences of the changes found in the cell mediated immunologic response are not yet clear.

One of the most worrisome problems concerns reproduction and child development. The effect on reproductivity is hard to assess because of the small number of cases reported with known exposure or known blood levels. Conception seems to be possible even in cases of overt poisoning, and pregnancy seems to follow a normal course. Early and late fetal losses may perhaps be related. The newborn child is extensively exposed to the chemicals through the mother, which leads to specific skin manifestations, to decreased birth weight, and retarded development with very high levels. Con-

genital anomalies have not been reported with the exception of disorders of tooth eruption and retarded growth for several years as a late manifestation in the case of overt poisoning. The immune response of the newborns has not been examined, though the rather high frequency of acute infections during the first year of life in Yusho children may point to an impairment of immune capability.

The concentration of the omniprevalent PCB in breast milk may lead to a high body burden of the infant. Although there still is no clear indication that the resulting levels pose significant health hazards, precautionary measures seem indicated.

On the whole, our view of the effects of the intake of PCBs and their contaminants still is rather blurred. But how could we get a clear picture on the clinical side? The determination of the intake, the actual body burden should be improved, taking advantage of the increased sensitivity of analytical methods for assessing evidence of absorption in man. Cinical symptomatology can then be estimated in relation to the kinetics of the chemicals in the body. Signs of physiological adjustments of organs and functions involved in the detoxification process should thereby not be considered adverse or irreversible health effects. Finally, long-term effects can only be evaluated by well planned and well conducted epidemiological studies.

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